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## The value of surveillance mammography of the contralateral breast in patients with a history of breast cancer

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### ABSTRACT

**Purpose:** To determine the contribution of surveillance mammography to the early detection of metachronous contralateral breast cancer (MCBC) and to assess its impact on the survival of breast cancer patients with relation to compliance.

**Method:** Breast cancer patients (5589) were identified using files from the regional cancer registry of the Comprehensive Cancer Centre North Netherlands (CCCN Groningen, The Netherlands). The programme sensitivity and the impact on prognosis of follow-up mammography with relation to compliance were evaluated in 114 patients who developed MCBC during hospital follow-up.

**Results:** The cumulative MCBC incidence rate at year 10 was 3.4% (95% CI: 2.8–4.0%). The programme sensitivity of surveillance mammography was 59.6% (95% CI: 50.6–68.7). In patients who complied with annual mammography, sensitivity was increased to 70.8% (95% CI: 61.7–80.0). Patients with MCBCs detected by routine mammography have better survival rates than patients with MCBCs detected by other means (HR: 3.18; 95% CI: 1.59–6.34). Though there was a trend towards improved survival in patients being compliant with regular clinical follow-up (HR: 1.69; 95% CI: 0.72–3.96), this was not the case for patients being compliant with annual mammography (HR: 1.02; 95% CI: 0.50–2.09).

**Conclusion:** Mammography is a valuable tool for the early detection of MCBC during hospital follow-up of breast cancer patients and is probably beneficial to survival. The utilisation of follow-up surveillance in breast cancer patients and its potential impact on survival deserve further investigation.

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## 1. Introduction

Contralateral breast cancer (CBC) is the most common second primary malignancy in patients with a history of breast cancer.<sup>1</sup> For metachronous contralateral breast cancer (MCBC) a constant annual incidence of 0.3–1.0% is observed.<sup>2–6</sup>

Contralateral surveillance mammography is recommended in the follow-up of patients treated for breast cancer and aims at early detection of MCBC to optimise the outcome.<sup>7–9</sup> Observational studies suggest that a secondary primary tumour detected before its symptomatic onset has a favourable impact on the survival of patients with MCBC.<sup>10,11</sup> However, the survival benefit of diagnosing MCBC by mammography has not yet been studied thoroughly.<sup>12,13</sup> Mammography surveillance in breast cancer follow-up has been shown to be underutilised, with the proportion of patients receiving a contralateral mammography varying from 80% in the first year to 60% in the fifth year of follow-up.<sup>14–16</sup> This study was designed to evaluate the diagnostic value of annual surveillance mammography and its impact on survival. In addition, the compliance with annual mammography was evaluated in MCBC patients, as was its potential impact on the diagnostic performance of mammography and MCBC patient survival.

## 2. Patients and methods

### 2.1. Settings and subjects

All the consecutive breast cancer patients diagnosed in four hospitals in the North Netherlands (an academic hospital, a large teaching hospital and two non-teaching hospitals) from January 1989 to January 2003 were selected from the files of the regional cancer registry of the Comprehensive Cancer Centre North Netherlands (CCCN Groningen, The Netherlands). This cancer registry contains data on diagnosis, stage and treatment, actively abstracted from the patients' medical records in all hospitals within the CCCN catchment area using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centres. Passive follow-up of the vital status through municipal population registries was conducted. The censoring date was 5th January 2007.

All women with newly diagnosed breast cancer were included. A new primary tumour was defined as any new tumour that is not a recurrence or a direct extension of a known tumour. All women with evidence of distant metastasis at the moment of primary diagnosis were excluded, as were patients who had a prior cancer other than non-melanoma skin cancer. A total of 5589 women were selected. The occurrence of any subsequent MCBC was ascertained by means of computerised record linkage. MCBC was defined as any contralateral breast cancer occurring at least 6 months after the first breast cancer. All other contralateral cancers were considered as synchronous bilateral breast cancers. Patients with synchronous bilateral breast cancer ( $N = 94$ ) were excluded from the cohort and thus the final cohort consisted of 5495 patients with primary ipsilateral breast cancer.

Of these 5495 women diagnosed with ipsilateral breast cancer, MCBC was reported in 139 patients during follow-up. For each of these patients, four to five patients without evidence of MCBC ( $n = 597$ ) – matched for hospital of diagno-

sis, age at first primary tumour and duration of follow-up – were selected randomly from the cohort. Follow-up information was retrieved actively from medical documents in hospitals for all 736 patients in our study. Follow-up information was not available for 67 patients (12 with MCBC and 55 without MCBC). For 13 patients, the MCBC was diagnosed after the hospital follow-up had ended, thus these MCBCs were not included in the evaluation of the contribution of surveillance mammography. Therefore, the study finally included 656 breast cancers with 114 occurrences of MCBC during hospital follow-up and 542 non-MCBCs.

### 2.2. Definitions

Surveillance mammography was defined as mammography undertaken with or without physical breast examination and other tests, in patients without any symptoms of relapse. The programme sensitivity of surveillance mammography was evaluated by calculating the number of MCBCs as detected by mammography divided by the total number of MCBC. Specificity was defined as the proportion of normal mammograms (BIRADS 1 and 2) out of the mammograms of the 542 patients without evidence of MCBC. All mammograms with BIRADS 3, 4 and 5 were considered as suspect for malignancy. In the case of BIRADS 3 the strategy was to perform additional diagnostics or to repeat the mammogram after 6 months, depending on the other patient characteristics. For mammograms without BIRADS classification, there was a classification with four categories (negative/benign/doubtful/malignancy). Negative and benign findings were categorised as BIRADS 1 and 2, doubtful findings which needed further tests were considered as BIRADS 3 or BIRADS 4, and those highly suggestive of malignancy were considered as BIRADS 5. The follow-up was considered as over when the patient was diagnosed with distant metastases, when there was a note in the files that the patient was discharged from further hospital follow-up, when the patient was referred to the National Breast Cancer Screening Programme, when the patient was transferred to a general practitioner for further follow-up or when the patient died. Overall survival and distant metastasis-free survival of MCBC patients were measured from the date of diagnosis of the first breast cancer.

Compliance with routine clinical examination and routine mammography was considered for patients with MCBC diagnosis. If the interval between the diagnosis of MCBC and the last clinical examination was less than or equal to the scheduled interval of clinical examinations (2–6 months in the first year; 4–8 months in the second year; 10–14 months in the following year), the patient was considered to be compliant with routine follow-up. If the interval between MCBC diagnosis and the previous mammography was less than or equal to 14 months, the patient was considered to be compliant with annual mammography.

Patients with MCBCs were divided into three groups by mode of detection. 'Routine mammography' consisted of patients with MCBC detected by mammography alone in routine follow-up. 'Routine others' consisted of patients with MCBC detected in other ways, usually physical examination, during routine follow-ups with or without mammography. 'Interval' consisted of patients with MCBC presenting between two scheduled follow-up appointments.

### 2.3. Statistical analysis

The incidence of MCBC and the confidence intervals (95% CIs) were calculated by the use of life tables. Both the sensitivity and the specificity of the mammography and their 95% CIs were calculated. Generalized estimating equations (GEEs) were used to estimate the 95% CIs for specificity estimates, which accounted for dependent outcomes among women who received more than one mammography during the study period. In addition, positive predictive values (PPVs) were calculated.

The mode of detection of MCBC was compared with  $\chi^2$  tests among groups with regard to the year of first tumour, patient age at MCBC, time to MCBC occurrence from first tumour and MCBC characteristics. Kaplan–Meier survival analysis was used to compare the overall and distant metastasis-free survival of the groups with regard to the mode of detection, compliance with routine follow-up visit and compliance with annual mammography. The association of mode of detection with the survival of MCBC patients was examined by a multivariate Cox proportional hazard model, adjusted for tumour characteristics at the first breast cancer and time from first tumour to MCBC. The impact (hazard ratios) of compliance with routine follow-up visits and annual mammography on survival was evaluated by univariate Cox proportional analysis.

## 3. Results

### 3.1. Incidence of MCBC

Of the 5495 women diagnosed with ipsilateral breast cancer, MCBCs were reported in 139 patients. The cumulative MCBC incidence rate at years 5 and 10 was 2.0% (95% CI: 1.6–2.4%) and 3.4% (95% CI: 2.8–4.0%), respectively (see Fig. 1).

### 3.2. Compliance, programme sensitivity and specificity of mammography

One hundred and fourteen MCBCs were included in the evaluation of the contribution of surveillance mammography of patients followed up in hospital. Nine (7.9%) patients were considered as not complying with routine clinical examina-

tions because they missed at least the former scheduled clinical examinations. Eighteen (15.8%) patients were considered as not complying with annual mammography because they missed at least the previous scheduled mammography.

The programme sensitivity of surveillance mammography was 59.6% (68/114; 95% CI: 50.6–68.7%; see Table 1). In the 105 patients complying with routine clinical examination, the sensitivity was 64.8% (68/105; 95% CI: 55.6–73.9%). In the 96 patients complying with annual mammography, the sensitivity was 70.8% (68/96; 95% CI: 61.7–80.0%). The specificity of mammography was 98.3% (95% CI: 97.9–98.7%).

### 3.3. Positive predictive values related to BIRADS scores (if available)

For 40% ( $n = 1392$ ) of the mammograms the BIRADS score was available. The PPVs for BIRADS 3, 4 and 5 were 0% (0/12), 25% (10/40) and 91% (19/21), respectively. The overall PPV for the mammograms with BIRADS classification regarding the presence of MCBC was 40% (29/73) which is somewhat higher than the PPV related to the mammograms without BIRADS classification (31%; 39/125).

### 3.4. Mode of detection

Forty-two (36.8%) MCBCs were detected by mammography alone. Thirty-three (29.0%) MCBCs were in the 'routine others' group, of which seven (6.2%) MCBCs were detected by physical examination alone, 26 (22.8%) were identified by both physical examination and mammography. Thirty-nine (34.2%) tumours were diagnosed as interval cancers.

There were trends indicating that MCBC was more likely to be detected by mammography in patients with the first tumour diagnosed after 1994 ( $\chi^2 = 15.075$ ,  $P = 0.005$ ) and in patients with MCBC at pathological T stage 1 or Tis ( $\chi^2 = 5.925$ ,  $P = 0.052$ ; see Table 2).

### 3.5. Comparison of MCBC patient survival by mode of detection

The patients with MCBC detected by mammography alone had better overall survival and distant metastasis-free survival rate than patients with MCBC detected by 'routine others' and 'interval'. (Log-rank = 11.598,  $P = 0.003$  and Log-rank = 10.401,  $P = 0.006$ , Figs. 2a and b).

Multivariate analysis indicates that the patients with MCBC detected by mammography have better survival rates than patients with MCBC detected by other means during routine follow-up (HR: 2.59; 95% CI: 1.17–5.75), and with MCBC arising as interval cases (HR: 3.63; 95% CI: 1.74–7.54). When we combined 'routine others' and 'interval', due to the overlap of the 95% CIs of the HRs, the HR of death was 3.18 (95% CI: 1.59–6.34) in patients with MCBC detected by other means compared to patients with MCBC detected by routine mammography alone. Patients with a first tumour at the pathological T2/3/4 stages have worse survival rates (HR: 1.90; 95% CI: 1.09–3.30) than patients with a first tumour at the pathological T1/Tis stage. Patients with involved lymph nodes at first tumour diagnosis have worse distant metastasis-free survival rates (HR: 1.91; 95% CI: 1.09–3.35) than those without involved

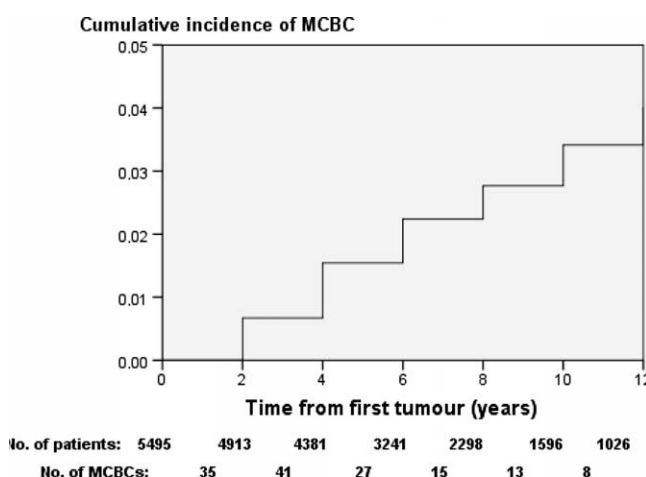


Fig. 1 – MCBC after primary treatment in ipsilateral breast cancer patients.

**Table 1 – Sensitivity of mammography in follow-up of breast cancer patients.**

Patients	n/N	Sensitivity	
		%	95% CI
All patients (programme sensitivity)	68/114	59.6	50.6–68.7
Compliant with routine clinical examination	68/105	64.8	55.6–73.9
Compliant with annual mammography	68/ 96	70.8	61.7–80.0

**Table 2 – Comparison of mode of detection for 114 MCBCs.**

Characteristics	Routine mammography (n = 42)	Routine others (n = 33)	Interval (n = 39)	$\chi^2$	P value
<i>Year of diagnosis of MCBC</i>					
1989–1993	1 (9)	2 (18)	8 (73)	15.075	0.005
1994–1998	19 (37)	21 (41)	11 (22)		
1999–2004	22 (42)	10 (19)	20 (39)		
<i>Time from first tumour</i>					
6 months	10 (39)	9 (34)	7 (27)	1.007	0.907
2 years	20 (37)	15 (28)	19 (35)		
5 years	12 (35)	9 (27)	13 (38)		
<i>Age group at MCBC</i>					
<50	5 (23)	6 (27)	11 (50)	4.359	0.628
50–59	11 (37)	9 (30)	10 (33)		
60–74	16 (40)	11 (28)	13 (32)		
75+	10 (45)	7 (32)	5 (23)		
<i>Pathologic T stage</i>					
pT1/Tis	36 (47)	19 (25)	22 (28)	5.925	0.052
pT2/3/4	5 (21)	11 (46)	8 (33)		
Missing	1 (8)	3 (23)	9 (69)		
<i>Pathologic N stage</i>					
N0	26 (36)	20 (27)	27 (37)	1.796	0.407
N+	10 (36)	11 (39)	7 (25)		
Missing	6 (46)	2 (15)	5 (39)		
<i>Histology</i>					
Invasive	36 (36)	31 (31)	33 (33)	1.691	0.429
Non-invasive	6 (43)	2 (14)	6 (43)		

lymph nodes. Patients with MCBC occurring earlier after the first tumour have worse overall and distant metastasis-free survival rates than patients with MCBC occurring later (HR: 0.86; 95% CI: 0.76–0.96 and HR: 0.86; 95% CI: 0.77–0.95, respectively; Table 3).

### 3.6. Comparison of MCBC patient survival by compliance

In addition, we evaluated the potential impact of compliance with routine clinical examinations and compliance with annual mammography on MCBC patient survival. Nine patients who missed at least the former scheduled clinical examinations showed worse survival (HR: 1.69; 95% CI: 0.72–3.96) and distant metastasis-free survival (HR: 1.91; 95% CI: 0.82–4.45) but neither result was statistically significant due to the small sample of non-compliant patients (see also Fig. 2c and d). There is no significant association of survival (HR: 1.02; 95% CI: 0.50–2.09) or distant metastasis free-survival (HR: 1.00; 95% CI: 0.19–2.04) with compliance with annual mammography in patients with MCBC. The survival curve of the compliant group was crossed with the one of non-compliant group (see Fig. 2e and f).

## 4. Discussion

This study is one of the largest studies to evaluate the impact of surveillance mammography on the survival of MCBC patients. The cumulative MCBC incidence rate at years 5 and 10 was 2.0% and 3.4%, respectively. The programme sensitivity of follow-up mammography was 60%. The patients with MCBC detected by mammography alone had better survival rates than patients with MCBC detected by other means with or without mammography ( $P = 0.004$ ). For patients complying with annual mammography, sensitivity was increased to 71%. Though there was a trend towards improved survival in patients being compliant with regular follow-up (HR: 1.69; 95% CI: 0.72–3.96), this was not the case for patients being compliant with annual mammography (HR: 1.02; 95% CI: 0.50–2.09).

Women diagnosed with a primary breast cancer are at increased risk of developing a second breast cancer. Markedly increased risks of MCBC have also been observed among breast cancer patients in many other studies.<sup>1,4,6,17</sup> The annual risk of developing MCBC remained constant at 0.3–0.4% per year after treatment in this series, which indicates that patients remain at risk of contralateral breast cancer for at



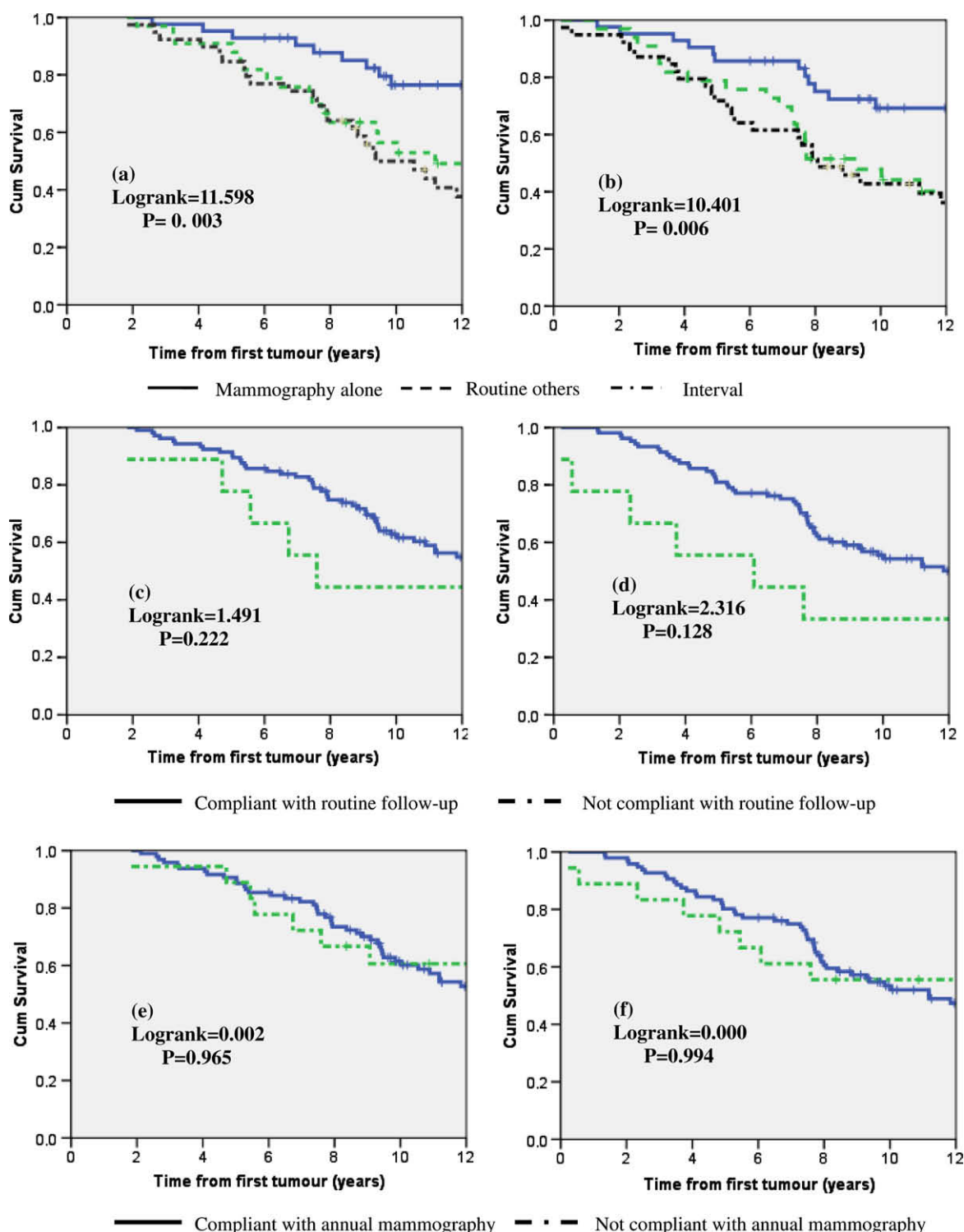


Fig. 2 – Survival (a, c, e) and distant metastasis-free survival (b, d, f) of patients with MCBC.

least ten years, which is consistent with findings in other studies.<sup>6</sup> This emphasises on the importance of surveillance and treatment of MCBC even at ten years after primary treatment to prevent the increased morbidity and mortality caused by MCBC.

We estimated the programme sensitivity of surveillance mammography to be 60% and the specificity to be 98%. These estimates are comparable with other studies, including stud-

ies of the breast cancer screening programme (sensitivity: 58–75%; specificity: 97–99%)<sup>18–20</sup> and studies of the follow-up of breast cancer survivors (sensitivity: 44%–70%).<sup>21–23</sup> Reported proportions of MCBC detected by mammography vary from 40% to 70% between studies because of dissimilarities in the patient populations, the frequency of mammography and MCBC case definition.<sup>2,21–23</sup> Due to the biological behaviour of tumours, some tumours will be missed by annual

**Table 3 – Multivariate Cox regression analysis of prognosis in patients with MCBC**

Factors	Hazard ratio	95% CI	P-value
Death			
Method of detection			
Routine mammography alone	1		0.003
Routine physical examination	2.59	1.17–5.75	
Interval	3.63	1.74–7.54	
Pathologic T stage of first tumour			
pT1/Tis	1		0.023
pT2/3/4	1.90	1.09–3.30	
Time between first tumour and MCBC (yrs)	0.86	0.76–0.96	0.008
Distant metastasis and Death			
Method of detection			
Routine mammography	1		0.011
Routine physical examination	2.09	1.00–4.37	
Interval	2.90	1.45–5.78	
Pathologic N stage of first tumour			
N0	1		0.023
N+	1.91	1.09–3.35	
Time between first tumour and MCBC(yrs)	0.86	0.77–0.95	0.004

mammography. In this study we were not able to review mammograms to assess whether cancers had been missed or should have been considered as real interval cancers, which can be considered as a limitation of the study. The proportion of MCBC detected by mammography alone was 37% in our study, which was less than the rate reported in the studies mentioned above. There was a trend that occurred in younger patients that MCBC is less likely to be detected by mammography, and the efficacy of mammography was also questioned in younger patients.<sup>23</sup> The patients in our series are relatively young than those in other studies, which could partly explain the lower proportion of MCBC detected by mammography alone.<sup>24</sup> We found a statistically significant association between the method of MCBC detection and the year of diagnosis. The proportion of MCBC detected in this study by mammography alone was higher when the patients developed MCBC after 1994. One review paper also implied that the contribution of mammography appeared to be of increasing importance over time.<sup>12</sup> A possible explanation for this could be technical improvements in mammography and the more effective use of mammography, as a consequence of the national guidelines on follow-up and the implementation of a national breast cancer screening programme in this country. Women with DCIS are at a 2–4-fold greater risk of developing cancer in the contralateral breast than women without prior DCIS.<sup>25</sup> Due to the limited number of patients with prior DCIS, we could not separately evaluate the value of surveillance mammography in women with prior DCIS.

Since 2000, there is a guideline in the Netherlands to use the BIRADS system. As a consequence, for about 60% of the mammograms the BIRADS score was not available in this study. The overall PPV for the mammograms with BIRADS classification regarding the presence of MCBC was 40% which is somewhat higher than the PPV related to the mammograms without BIRADS classification (31%). The higher PPV in mammograms with a BIRADS classification might be a reflection of an improved classification. The higher the BIRADS score, the higher the related PPV. It should be mentioned

that the follow-up information was collected only for a stratified sample of this population ( $n = 656$ ), including all patients with a MCBC and a selection of patients without MCBC. As a consequence, this sample does not give a reflection of the true prevalence of MCBC, which was only 2.5% (139/5495) in the original sample. It can be expected that the PPV will be lower in clinical follow-up practice.

The tumour size of MCBC detected by mammography alone was smaller than that found for 'routine others' and 'interval' cases, as expected, though the differences were not statistically significant, probably due to the reduction of sample size by missing values. The proportion of smaller tumours (less than 2 cm) was much higher (86%) in MCBC detected by mammography, which accords with the study by Samant and colleagues.<sup>2</sup> We did not find any significant difference in the histological characteristics of MCBC between the patients with MCBC detected by mammography and other methods.

The characteristics of the primary tumour were associated with the overall survival rate and the distant metastasis-free survival rate of MCBC patients. The mode of detection of MCBC remained significantly associated with both the overall survival rate and distant metastasis-free survival rate in MCBC patients after adjustment for the first primary tumour characteristics, which indicated that the impact of detection mode on survival could not be explained by any difference in the pathological stage of the first tumour.<sup>21,26</sup> A population-based study revealed that MCBC at stage II or higher worsens the patient survival rate whereas the MCBC at stage I does not.<sup>27</sup> As with earlier diagnosis of first tumours, the early detection of MCBC was associated with an 81% reduction in risk of breast cancer death in the SEER database.<sup>28</sup> We presume the impact of the mode of detection of MCBC on survival was mainly due to the early detection of MCBC by mammography. Additionally, our results indicate that the interval between MCBC occurrence and the first tumour was associated with MCBC patient survival, which is in line with another study.<sup>29</sup> The goal of surveillance mammography not

only includes the early detection of MCBC but also the early detection of ipsilateral tumour recurrences. One review found that 30% of all ipsilateral tumour recurrences were detected by mammography in patients after breast conserving surgery; however, no significant reduction of mortality was found in patients with ipsilateral tumour recurrences detected by mammography.<sup>12</sup> Further research is warranted to investigate the impact of mammography on survival with regard to early detection of ipsilateral tumour recurrence.

Although the benefit of mammography is unbiased by lead time because survival was measured from the first primary breast cancer, a length bias is unavoidable in studies comparing mammography detected cancers with interval cancers. The slow-growing MCBCs are more likely to be detected by mammography. Nevertheless, although length bias was also claimed to affect the evaluation of mammographic efficacy in the breast cancer screening programme, periodic mammography was well accepted as the most cost-effective method for screening for breast cancer in many countries, supported by evidence from randomized controlled studies.<sup>30</sup> Therefore, although the observed survival improvement associated with the mode of detection of MCBC might be partially explained by length bias, it appears that surveillance mammography is effective for the early detection of MCBC and for improving those patients' survival.

Competing risk is always an issue when investigating the prognostic factors of one disease with all-cause mortality. The patients could die from diseases other than breast cancer. It is reasonable to suppose that older patients are more likely to die due to competing risks. However, patients with MCBC detected by mammography alone were not younger than those in the 'routine others' and 'interval' groups. The findings were also not reversed when distant metastasis was taken into account as a substitute for breast cancer specific mortality. Therefore, competing risk is unlikely to explain the better survival in mammography detected MCBC patients.

Eighteen patients did not receive annual mammography in the preceding 14 months. In other words, the interval between the tumour detection and the last mammography was greater than 1 year for these patients. It is possible that MCBCs were detected early by mammography where patients complied with annual mammography. In this study, we found a trend indicating that the sensitivity of mammography was improved in patients being compliant with routine clinical examinations and patients being compliant with mammography. There was a trend of improvement of prognosis in patients who complied with routine follow-up, though the differences were not statistically significant, probably due to the small sample size of non-compliant patients. Regarding compliance with mammography, we did not find a significant association between the compliance with annual mammography with the prognosis of patients with MCBC, despite the 11% (from 59.6% to 70.8%) improvement in the sensitivity of annual mammography. Though annual mammography could improve the early detection of MCBC and could improve the chances of improving survival, it is not yet clear that the detection of MCBC by mammography will result in better survival, due to the varying behaviour of tumours and the characteristics of patients. The cohort in this study, though very large in comparison to previous studies, is still too small to

answer these important questions. Our findings indicate that the 11% improvement in sensitivity in compliant patients is unlikely to be sufficient to reduce mortality among women with MCBC, which is in line with another study.<sup>31</sup> The same analysis should be repeated with a much larger cohort of women. A generally considered disadvantage of routine follow-up is that patients who had suspicious symptoms wait for their clinic visit rather than going to hospital, which probably worsens prognosis. Patients should be strongly advised to see their doctors whenever suspicious symptoms are found.<sup>7,8</sup>

In summary, the risk of contralateral breast cancer remains constant after primary breast cancer, even after 10 years at 0.3–0.4% per year. During routine follow-up, this study convincingly shows that mammography can identify MCBC at an early stage and thereby improve the survival of these patients. Mammography is a valuable tool for the early detection of MCBC during hospital follow-up of breast cancer patients and is probably beneficial to survival. The utilisation of follow-up surveillance in breast cancer patients and its potential impact on survival deserve further investigation.

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## Conflict of interest statement

None declared.

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